REMARKS

Upon entry of the present amendment, claims 15 and 16 are pending in this application. Claims 1-4, 7-10 and 12-14 have been cancelled. Applicants reserve right to pursue the subject matter of these claims in a continuing application(s). Claims 15 and 16 have been added. Support for these claims can be found in cancelled claims 1 and 13 and throughout the specification (*See*, for example, page 22, line 3). No new matter is added.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Howard B. Haimes.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejection

Claims 1-4, 7-10 and 12-14 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the specification does not support a method of treating, ameliorating or preventing hypertension or systolic hypertension by administering the claimed combination as the Examiner alleges the specification only provides support for the claimed combination thereby only when it is used to treat cardiovascular therapies (antioxidants), or heart failure, cardiomyopathy or heart attack or atherosclerosis. *See*, Office Action at page 3. Applicants have cancelled claims 1-4, 7-10 and 12-14. Applicants traverse the rejection as it applies to new claims 15 and 16.

New claims 15 and 16 are drawn to methods and formulations for treating, ameliorating or preventing isolated systolic hypertension with the combination of 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride and hydrochlorothiazide. Applicants submit that page 18, line 21 - page 19, line 31 and page 21, line 23 - page 22, line 11 (more specifically page 22, lines 8-11) provide sufficient written description for pending claims 15 and 16.

Specifically, page 18, line 21 - page 19, line 31 (more specifically page 19, lines 8-10) provide sufficient written description for **first** agents of the invention (*i.e.*, 3-(2-phenyl-

2-oxoethyl)-4,5-dimethylthiazolium chloride) to treat, ameliorate or prevent isolated systolic hypertension and further provide support that the first agents of the invention can be combined with additional (*e.g.*, second) agents (**"Emphasis Added"**). Moreover, page 21, line 23 - page 22, line 11 (more specifically page 22, lines 8-11) provide written description for first agents for administration or in a combined formulation with second agents (*i.e.*, diuretics) with a preferred diuretic being hydrochlorothiazide (page 22, line 3).

Applicants disagree with the Examiner's assertion that the specification supports these combinations only for the treatment of heart failure, cardiomyopathy or heart attack. One of ordinary skill in the art would readily recognize that the essential manifestation of these disorders of which to direct treatment is isolated systolic hypertension (Kannel et al., *N. Eng. J. Med.* 287: 781-787, 1972; Drayer et al., *Arch. Intern. Med.* 124: 160-164, 1969; Rabkin et al. *Ann. Intern. Med.* 88: 342-345, 1978; Kannel et al., *J. Am Med. Assoc.* 245: 1225-1229, 1981; Multiple Risk Factor Intervention Trial Research Group, *J. Am Med. Assoc.* 248: 146-147, 1982; Smulyan and Safar, *Ann. Intern. Med.* 132: 233-237, 2000). Further, the Examiner refers to Goodman & Gilman's, *The Pharmacological Basis of Therapeutics*, 9th Ed., McGraw-Hill Companies, NY, Ch. 33, pgs. 780-805, 1996 and states (*See*, Office Action page 5) the agents recited in page 21, line 23 - page 22, line 11 (*i.e.*, diuretics) are used for treating hypertension. Thus, Applicants submit that based on the state of the art at the time of filing and the disclosure in the specification at page 18, line 21 - page 19, line 31 and page 21, line 23 - page 22, line 11 one of ordinary skill in the art would readily conclude that at the time the application was filed, Applicants had possession of the invention as claimed. *See*, Haimes Declaration ¶ 4.

Applicants respectfully request withdrawal of the present rejection.

35 U.S.C. § 103 Rejection

Claims 1-4, 7-10 and 12-14 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,853,703 to Cerami ("Cerami") in view of Goodman & Gilman's, The Pharmacological Basis of Therapeutics ("Goodman"). The Examiner states that it would have been obvious to combine the thiazolium compounds of Cerami with the known anti-hypertensive agents taught by Goodman because one of ordinary skill in the art

would reasonably expect the additive affect of the compounds to be effective in treating hypertension. *See*, Office Action at pages 4-6. Applicants have cancelled claims 1-4, 7-10 and 12-14. Applicants traverse the rejection as it applies to new claims 15 and 16.

New claims 15 and 16 are drawn to methods and formulations for specifically treating, ameliorating or preventing isolated systolic hypertension with the specific combination of 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride and hydrochlorothiazide.

Applicants submit that there is no suggestion or motivation to combine the teachings of Cerami and Goodman to reach the specific thiazolium and diuretic species combination of pending claims 15 and 16. Specifically, it is well recognized under U.S. law that "the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious" *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) and the Federal Circuit has declined to state the rule that "regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it" *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992); *Merck & Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804 (Fed. Cir. 1989).

The Examiner states that Cerami does not specifically teach the administration or formulation of 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride but states that it falls within the claimed genus and is similar to 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium bromide which is specifically disclosed and thus it is obvious that it would be effective in treating hypertension. *See*, Office Action at page 6. This is in direct contradiction of the decisions cited *supra* and M.P.E.P 2144.08 which states that the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.

The Examiner also states that modification to combine these anti-hypertensive agents all of which are known to be useful for the same purpose, would have been obvious to one of ordinary skill in the art. *See*, Office Action at page 5. A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d at 493. Further, "The consistent

criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

The ordinary skilled artisan has no reasonable expectation of success combining Cerami and Goodman to reach the present invention. The Examiner assertion is based on the assumption that any anti-hypertensive agent can be combined with any other anti-hypertensive agent to produce an additive effect in the treatment of hypertension. *See*, Office Action page 5. This assertion is incorrect. In fact, several of the oldest and most widely used anti-hypertensive agents (*i.e.*, Methyldopa, Clonidine, Reserpine) are not readily combined with other anti-hypertensive agents to treat hypertension and combinations of these anti-hypertensive agents have numerous detrimental side effects (Veterans Administration Cooperative Study Group on Antihypertensive Agents, *J. Am Med. Assoc.* 202: 1028-1034, 1967; Veterans Administration Cooperative Study Group on Antihypertensive Agents, *J. Am Med. Assoc.* 213: 1143-1152, 1970; Hypertension Detection and Follow-Up Program Cooperative Group, *J. Am Med. Assoc.* 242: 2562-2577, 1979; Houston, *Prog. Cardiovasc. Dis.* 23: 337-350, 1981). *See*, Haimes Declaration ¶ 7.

Using references available on the filing date of the instant application, one of ordinary skill in the art would not reasonably expect that any anti-hypertensive agent could be combined any other anti-hypertensive agent to produce an additive effect in the treatment of hypertension and certainly not to specifically treat isolated systolic hypertension. Further, one of ordinary skill in the art reading the thiazolium disclosure of Cerami which does not specifically teach the administration or formulation of 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride, would not combine that disclosure with the general anti-hypertension disclosure of Goodman to reach the specific thiazolium and diuretic species combination of the pending claims 15 and 16 to treat isolated systolic hypertension with a reasonable expectation of success. *See*, Haimes Declaration ¶ 8.

For the foregoing reasons, Applicants submit that the skilled artisan would not be motivated to combine Cerami and Goodman to reach the present invention.

Long-Felt But Unsolved Need

Moreover, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made involves factual findings with respect to secondary considerations, including long-felt but unsolved need. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

There has been a long-felt but unsolved need for methods or formulations that safely and specifically treat, ameliorate or prevent isolated systolic hypertension in a subject. Currently, essential hypertension is treated by numerous anti-hypertensive agents (*e.g.*, diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, etc.). *See*, Goodman & Gilman's, pgs. 780-805. These treatment methods utilizing the traditional anti-hypertensive agents indiscriminately decrease systolic and diastolic blood pressure (Cruickshank et al., *Lancet* 1: 581-584, 1987). Isolated systolic hypertension is quite different from essential hypertension and is defined as systolic blood pressure higher than 160 mm Hg with a diastolic blood pressure of 90 mm Hg or lower (Koch-Weser, *Am. J. Cariol.* 32: 499-510, 1973). It is the normal or low diastolic pressure that is the defining characteristic that makes isolated systolic hypertension different from essential hypertension. *Id.* Treatment with traditional anti-hypertensive agents lower the increased systolic blood pressure but concomitantly lowers the already low diastolic blood pressure in subjects with isolated systolic hypertension. This simultaneous lowering of low diastolic pressure leads to the controversial J-curve phenomenon and the compromise of coronary perfusion (Cruickshank et al., *Lancet* 1: 581-584, 1987). Thus there is a long-felt but unsolved need for methods and formulations which are able to specifically treat isolated systolic hypertension by lowering increased systolic blood pressure but which eliminate or safely limit a decrease in already low diastolic blood pressure. *See*, Haimes Declaration ¶ 9.

Increased vascular stiffness and the resulting reduced vascular compliance are the critical factors which underlies the pathogenesis of isolated systolic hypertension. The reduced vascular compliance leads to an increase in pulse pressure and pulse wave velocity, which is associated with an earlier and enhanced reflection of pressure waves from the periphery that results in increase of systolic blood pressure, while the diastolic blood pressure deceases, resulting in increased pulse pressure (Darne et al., *Hypertension* 12: 392-

400, 1989; Madhavan et al., *Hypertension* 23: 395-401, 1994; Safar et al., *J. Hypertens.* 18: 1159-1163, 2000; Safar et al., *Stroke* 31: 782-790, 2000). Thus, there is a long-felt but unsolved need for methods and formulations which are able to improve vascular compliance which would lower systolic blood pressure without simultaneously lowering diastolic blood pressure in subjects with isolated systolic hypertension. *See*, Haimes Declaration ¶ 9.

The present invention solves this long felt need by combining hydrochlorothiazide with 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride which, different than other anti-hypertensive agents that only generally improve vascular compliance, directly reduces vascular stiffness and the resulting reduced vascular compliance. This direct action, along with decreasing systolic blood pressure, can increase the mean and even the minimum diastolic blood pressure. Thus, Applicants submit that methods and formulations combining a specific compound (3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride) that directly decreases increased vascular compliance with a specific general anti-hypertensive diuretic (hydrochlorothiazide) solve a long-felt but unsolved need in the art by decreasing increased systolic blood pressure without simultaneously decreasing already low diastolic pressure thus avoiding the dangerous J-curve phenomenon and the compromise of coronary perfusion in patients. *See*, Haimes Declaration ¶ 10.

Withdrawal of this rejection is respectfully requested.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and a Notice of Allowance for the pending claims is respectfully requested. If there are any questions regarding this application that can be handled in a phone conference with Applicants' Attorneys, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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